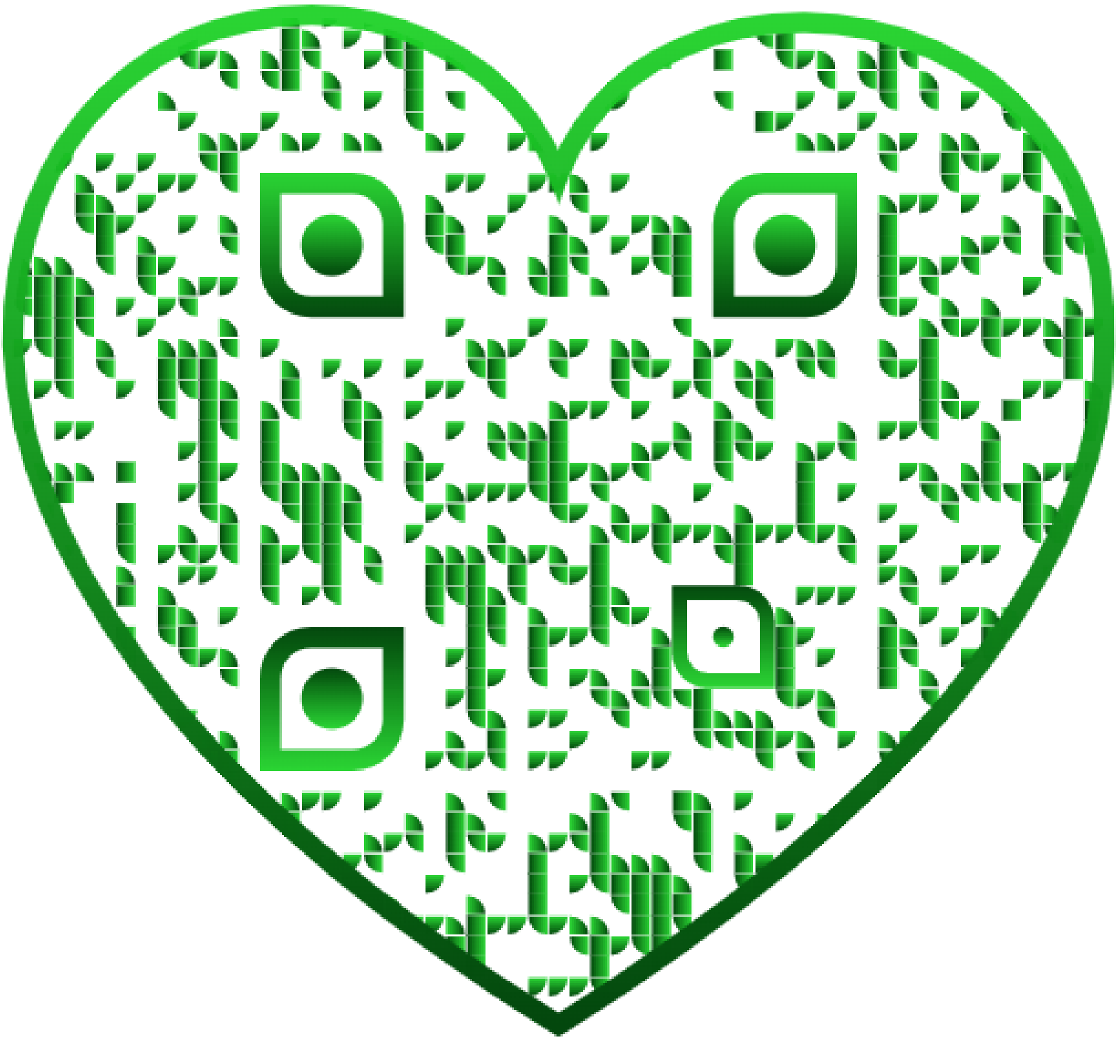
  - ✓ In children prolonged deficiency can lead to poor brain development.
- Patients with unexplained **neuropathies** should be evaluated for vitamin B_{12} deficiency.
- Labs: MCV is elevated >100 fL, low serum vitamin B_{12} level (<150 pg/mL), low Hct. **Elevations in MMA** are more specific for vitamin B_{12} deficiency. **Homocysteine** is also elevated in several other situations including: folate deficiency, chronic renal disease, alcoholism, smoking, use of steroid or cyclosporine therapy
- Treatment
  - ✓ Goals
    - ↳ Reversal of hematologic manifestations
    - ↳ Replacement of body stores
    - ↳ Prevention or resolution of neurologic manifestations
  - ✓ 1,000 mcg of cyanocobalamin daily IM for 1 week, thereafter weekly for 1 month and monthly thereafter for maintenance.
  - ✓ Parenteral therapy is preferred for patients exhibiting neurologic symptoms until resolution of symptoms and normalization of hematologic indices
  - ✓ When patients are converted from the parenteral to the oral form of cobalamin, 1,000 mcg of oral cobalamin daily can be initiated on the due date of the next injection
  - ✓ B_{12} should be continued *for life* in pernicious anemia.

C) Folic Acid Deficiency Anemia

- Poor eating habits make this deficiency more common for elderly patients, teenagers whose diets consist of "junk food," alcoholics, food faddists, the impoverished, and those who are chronically ill or demented. Folic acid absorption may decrease for patients who have malabsorption syndromes or those who have received certain drugs.
- In alcoholics with poor dietary habits, alcohol interferes with folic acid absorption, interferes with folic acid utilization at the cellular level, and decreases hepatic stores of folic acid.
- Recommended daily allowance
  - ✓ Nonpregnant females: 400 mcg
  - ✓ Lactating females: 500 mcg
  - ✓ Pregnant females: 600 mcg
- **Treatment:**
  - ✓ Folic acid supplementation at a dose of 400 mcg daily is recommended for all women.
  - ✓ Women who have previously given birth to offspring with neural tube defects or those with a family history of neural tube defects should ingest 4 mg daily of folic acid.



D) Anemia of Inflammation

- AI is both ACD and anemia of critical illness
- The onset of anemia of critical illness is quicker, over days, and typically occurs in a hospital setting.
- ACD has a similar mechanism, but it develops over months to years from a chronic condition.
  - ✓ *Chronic disease:* TB, lung abscess, bronchiectasis, HIV, bacterial endocarditis, osteomyelitis, UTI
  - ✓ *Chronic* inflammation: rheumatoid arthritis, SLE, IBD, gout
  - ✓ Malignancy: carcinoma, lymphoma, leukemia, multiple myeloma
  - ✓ Less common causes: alcoholic liver disease, CHF, thrombophlebitis, COPD, IHD
- Factors that may contribute to anemia in critically ill patients include, sepsis, frequent blood sampling, surgical blood loss, immune-mediated functional iron deficiency, decreased production of endogenous EPO, reduced RBC life span, active bleeding
- *Labs:* decreased serum iron level, *serum* ferritin level is normal or increased, TIBC is decreased.
- *Treatment:*
  - ✓ Transfusion (Hb < 7 to 8 g/dL)
  - ✓ ESAs have been used to stimulate erythropoiesis for patients with AI since a relative EPO deficiency exists for the degree of anemia. Two agents are available: recombinant epoetin alfa and recombinant darbepoetin alfa
    - ➢ Epoetin alfa: 50 to 100 units per kilogram three times per week
    - ➢ Darbepoetin alfa: 0.45 mcg per kilogram once weekly

Follow-Up Evaluation

- Monitor the CBC monthly, monitor symptom resolution. A 1.0-g/dL per week increase in Hb is desirable in patients with IDA. Reevaluate patients with increases less than 2.0 g/dL in 3 weeks. For patients with folic acid deficiency, monitor Hb periodically and reevaluate patients who fail to normalize Hb levels after 2 months of therapy.[1]
- Monitor side effects of therapy
  - ✓ Oral iron: nausea, vomiting, abdominal pain, heartburn, constipation, and dark stools
  - ✓ Parenteral iron: anaphylaxis (test dose required for iron dextran and observe for 1 hour after), injection-site pain/irritation, arthralgias, myalgias, flushing, malaise, and fever

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[1] Chisholm-Burns MA, Wells BG, Schwinghammer TL: **Pharmacotherapy principles and practice**: McGraw-Hill; 2016.

- ✓ Folic acid: bad taste and nausea, rash, and allergic reactions
- ✓ Vitamin B_{12}: pain and erythema at injection site
- ✓ ESAs: hypertension (monitor BP), thrombosis (eg, DVT/PE, MI, CVA and TIA), arthralgias, and headache

6.2. Coagulation and Platelet Disorders

Hemophilia

✍ Hemophilia A and B are coagulation disorders that result from defects in the genes encoding for plasma coagulation proteins.

✍ **Classification**

- Hemophilia A (Classic hemophilia): caused by the deficiency of factor **VIII**
- Hemophilia B (Christmas disease): caused by the deficiency of factor **IX**.
- The incidences of hemophilia A and B are estimated at 1 in 5000 and 1 in 30,000 male births, respectively.
- Both types of hemophilia are evenly distributed across all ethnic and racial groups

✍ **Pathophysiology**

- The pathophysiology of hemophilia is based on the deficiency of factor VIII or IX → inadequate thrombin generation → impaired intrinsic-pathway coagulation cascade.
- Factor VIII and IX genes are located on the X chromosome. Hemophilias are recessive X-linked diseases.

> **Key Concepts** *Generally, affected males carrying either defective allele on their X chromosome do not transmit the gene to their sons. However, their daughters are obligate carriers*

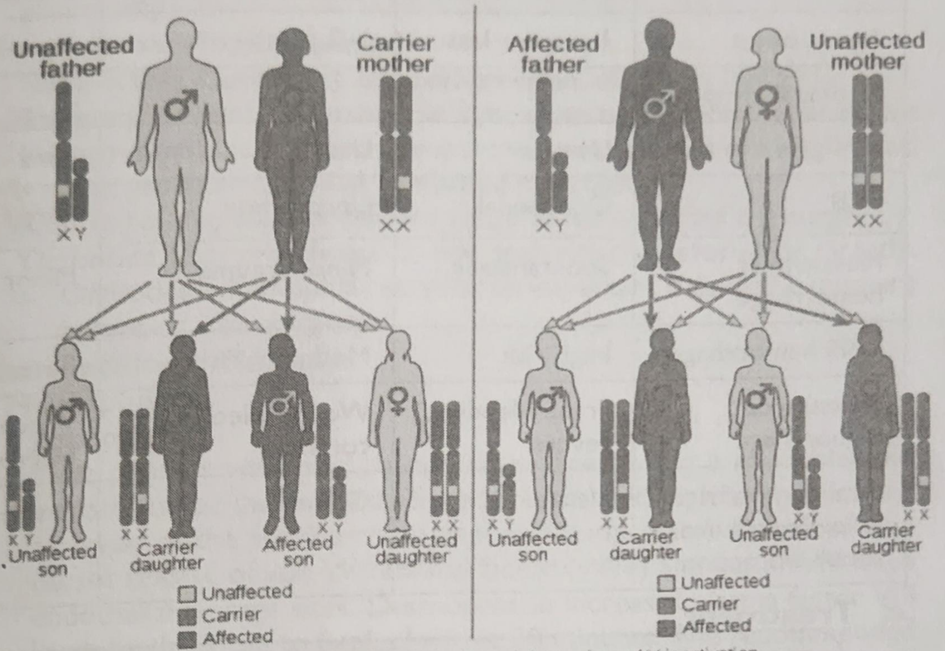
- Generally, affected males carrying either defective allele on their X chromosome do not transmit the gene to their sons. However, their daughters are obligate carriers.

- More than 1000 mutations in factor VIII and IX genes have been identified to cause clinical hemophilia. Consequently, hemophilia is not a result of a single genetic mutation. However, inversion at intron 22 of the factor VIII gene accounts for 40% of severe hemophilia A cases. Owing to the high incidence, this mutation is used for carrier and prenatal testing.

✍ **Signs and Symptoms**

- Ecchymoses(palpable/raised), hemarthrosis (especially knee, ankle, and elbow)
- Joint pain, joint swelling and erythema, decreased range of motion
- Muscle hemorrhage, swelling at the site of muscle bleeding, pain with motion of affected muscle

- Signs of nerve compression, significant anemia from an iliopsoas bleed
- Oral bleeding with dental extractions or trauma
- Hematuria, intracranial hemorrhage (spontaneous or following trauma)
- Excessive bleeding with surgery


Unaffected father
XY
Carrier mother
XX
Affected father
XY
Unaffected mother
XX
XY
Unaffected son
XX
Carrier daughter
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Affected son
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Unaffected daughter
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Unaffected son
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Carrier daughter
XY
Unaffected son
XX
Carrier daughter
☐ Unaffected
▨ Carrier
■ Affected
☐ Unaffected
▨ Carrier
■ Affected

Note: a few carriers may be mildly affected due to skewed X-inactivation.

Figure 6.1. Inheritance of Hemophilia

Laboratory Testing

- Prolonged activated partial thromboplastin time (aPTT)
- Decreased factor VIII or factor IX level
- Normal prothrombin time (PT)
- Normal platelet count
- Normal von Willebrand factor antigen and activity
- Normal bleeding time

Diagnosis

- Male with unusual bleeding
- Family history of bleeding
- Brothers of patients with hemophilia should be screened; sisters should undergo carrier testing
- Prolonged partial thromboplastin time (aPTT)
- A decreased FVIII or FIX level

Complications of Hemophilia

Table 6.2. Complications of hemophilia[1]

Complications	Severe (< 0.01 IU/mL)	Moderate (0.01–0.05 IU/mL)	Mild (>0.05 IU/mL)
Age at onset	1 year or less	1–2 years	2 yrs–adult
Neonatal symptoms			
ICH	Usual	Usual	Rare
PCB	Occasional	Uncommon	Rare
Muscle/joint hemorrhage	Spontaneous	Minor trauma	Minor trauma
CNS hemorrhage	High risk	Moderate risk	Rare
Postsurgical hemorrhage	Frank bleeding, severe	Wound bleeding, common	Wound bleeding
Oral hemorrhage following trauma, tooth extraction	Usual	Common	Common

Treatment

Key Concepts *Currently, there is no cure for hemophilia A or B. The life expectancy of hemophiliacs was only 8 to 11 years in the 1920s and 1930s. With the development of effective treatment strategies, life expectancy is currently about 63 to 75 years, nearly that of the normal population.*

- **Desired Outcomes**
  - ✓ Decrease the number of bleeding episodes per year or bleeding frequency
  - ✓ Normalize or improve clotting factor concentrate levels
  - ✓ Maintain clinical joint function
  - ✓ Maintain quality-of-life measurements
- **General Approach to Treatment**
  - ✓ Intravenous factor replacement to treat or prevent bleeding is the primary treatment of hemophilia.

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[1] Trinkman H, McCavit TL, Duran L. Coagulation Disorders. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Michael Posey LL. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e. McGraw Hill; 2023. Accessed January 29, 2023

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- ✓ Primary prophylaxis: the regular administration of factor concentrates with the intention of preventing joint bleeds. The rationale for primary prophylaxis is that individuals with factor levels of greater than 0.02 IU/mL rarely suffer from *spontaneous bleeds* and *arthropathy*

- **Nonpharmacologic Therapy**
  - ✓ **Supportive Care**: Rest, ice, compression, elevation (RICE)
  - ✓ **Surgery**: Surgical arthroscopic synovectomy reduces replacement therapy–resistant disease and repetitive hemarthrosis of a single joint.
    - ➯ This procedure removes inflamed joint tissue.
    - ➯ Patients may have decreased range of motion after the surgery.
  - ✓ **Orthotics**: Joint prostheses do not deal with the deformities directly.
    - ➯ Orthotics in hemophilia serve as an important supportive measure before or after surgery
- **Pharmacologic Therapy**
  - **a) Hemophilia A**
    - *i) Desmopressin*
    - ➯ Most patients with mild to moderate disease and a minorbleeding episode can be treated with desmopressin acetate. It is the synthetic analogue of the antidiuretic hormone (vasopressin). Desmopressin causes release of von Willebrand factor (vWF) and factor VIII from endothelial storage sites. Desmopressin increases plasma factor VIII levels by threefold to fivefold within 30 minutes. The recommended dose is 0.3 mcg/kg IV (in 50 mL of normal saline infused over 15–30 minutes) or SC (in < 1.5 mL) or 150 to 300 mcg intranasally via concentrated nasal spray, may repeat after 24 hours.
    - *ii) Factor VIII Replacement*
    - ➯ Patients with severe hemophilia may receive primary (before the first major bleed) or secondary (after the first major bleed) prophylaxis.
    - ➯ All hemophiliacs with a major bleed require factor VIII replacement.
    - ➯ The therapy may include: recombinant (produced via transfection of mammalian cells with the human factor VIII gene) or plasma-derived (concentrate from pooled plasma) factor VIII.
  - **b) Hemophilia B**
    - ✓ *Factor IX Replacement*
    - ➯ Hemophilia B therapy may include recombinant (produced via transfection of mammalian cells with the human factor IX gene) or plasma-derived (concentrate from pooled plasma) factor IX
    - ➯ Because it is a small protein, the factor IX molecule passes into both the intravascular and the extravascular spaces. Therefore, the

volume of distribution of recombinant factor IX is twice that of factor VIII.

✓ Pain Associated with Hemophilia

- Pain commonly occurs in patients with hemophilia. Acute bleeding episodes and long-term joint destruction are common sources of pain. Acetaminophen and opioid analgesics are recommended to control mild to moderate and severe pain, respectively.
- Nonsteroidal anti-inflammatory drugs and aspirin should be avoided if possible, because these drugs bind to platelets and increase the risk of bleeding episodes. Cyclooxygenase-2 inhibitors can be used with caution.[1]

von Willebrand Disease

- **von Willebrand disease (vWD)** is the most common inherited bleeding disorder caused by a deficiency or dysfunction of vWF. The disease prevalence is estimated at 30 to 100 cases per million. In contrast to hemophilia, the majority of vWD cases are inherited as an autosomal dominant disorder, ensuing equal frequency in males and females.
- Two main functions in hemostasis: to aid platelet adhesion to injured blood vessel walls and to carry and stabilize factor VIII in plasma
- **Clinical Presentation**
  - Symptoms: bruising, mucocutaneous bleeding, epistaxis, oral cavity bleeding, menorrhagia, GI bleeding, joint and deep tissue bleeding, postoperative bleeding
- **Management**
  - Nonpharmacologic Therapy

✓ Local measures, including pressure and ice, may be used to control superficial bleeding.

a) Desmopressin: most patients with type I vWD (functionally normal vWF) and a minor bleeding episode can be treated successfully with desmopressin. It induces release of factor VIII and vWF from endothelial cells through interaction with vasopressin V2 receptors.
   - A test dose administered at the time of diagnosis

b) Replacement therapy

✓ Indications
   - Type I patients unresponsive to desmopressin,
   - Patients with type 2 and 3 vWD,
   - Major surgery patients

✓ Product: plasma-derived virus-inactivated factor VIII concentrates containing vWF

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[1] MASAC, Recommendations on Use of COX-2 Inhibitors in Patients with Bleeding Disorders. MASAC Document #162. New York: National Hemophilia Foundation, 2005

Immune Thrombocytopenic Purpura (ITP)

- ITP is one of the most common causes of acquired thrombocytopenia
- Incidence is 1.9 to 6.4 cases per 100,000 persons in children and 3.3 cases per 100,000 in adults.
- ITP is an autoimmune disorder caused by the binding of antibodies (usually immunoglobulin G [IgG]) to platelet surface antigens, resulting in shortened platelet life span.
- Childhood-onset and adult-onset ITP present very differently. **Adult-onset ITP** is generally chronic (> 6 months) and affects women two to three times more often than men. **Childhood-onset ITP** is acute in onset, usually follows an infectious illness, both sexes are equally affected. It resolves on its own within 4 to 6 weeks without major sequelae.
- **Pathophysiology**
  - In ITP, IgG autoantibodies bind to platelet-antigen complex and are cleared from the blood via binding to mononuclear phagocytes by macrophage Fcγ receptor leading to thrombocytopenia.
  - Platelet survival time is significantly shorter in patients with ITP (from minutes to 2–3 days compared with normal 7–10 days).
  - Sequestration in spleen, liver, and bone marrow is partially responsible for decreased platelet survival
- **Clinical Presentation**
  - Symptoms: petechiae, purpura, wet purpura, ecchymoses, cutaneous bleeding, mucosal site bleeding, epistaxis, gingival bleeding, hematuria, menorrhagia, intracranial hemorrhage (rare)
- **Diagnostic Criteria**
  - Platelet less than 100 × 103/mm3, otherwise normal CBC with differential
  - Normal peripheral blood smear (no hemolysis or blast cells)
  - History and physical exam ruling out other possible causes of thrombocytopenia count
- **Treatment**
  - Desired outcome: to maintain the platelet count associated with sufficient hemostasis (> 30 × 10^3/mm^3)
  - General Approach
    - ✓ The initial treatment of children with ITP is controversial because > 75% to 80% of cases resolve spontaneously irrespective of pharmacologic intervention. Therapy may be considered in children meeting one of the following criteria:
      - Platelet counts <10 × 10^3/mm^3 and mucocutaneous bleeding;
      - Platelet counts <30 × 10^3/mm^3 and moderate systemic or mucosal bleeding; or factors that may increase the risk of bleeding (such as participation in active contact sports increasing risk of head injury)

  - ✓ In adults, treatment is indicated when platelet counts are <30 × 10^3/mm^3
- ***Glucocorticoids***
  - ✓ Decrease splenic sequestration of antibody-coated platelets, diminish antibody generation by the spleen and the bone marrow, and increase platelet output by the bone marrow.
  - ✓ In adults, the response rate to oral prednisone (1 mg/kg/day) is 50% to 75%, with patients usually responding within the first 1 to 2 weeks.
  - ✓ Duration of therapy: prednisone therapy for 21 days, followed by a taper.
  - ✓ High-dose dexamethasone (40 mg orally or IV daily) administered for 4 to 8 days

REVIEW QUESTIONS

1. The leading cause of anemia worldwide is:
   A. Anemia of chronic disease B. Iron deficiency anemia
   C. Folic acid deficiency anemia D. Vit B_{12} deficiency anemia
2. Which one is correctly matched?
   A. Iron deficiency: macrocytic anemia
   B. Folic acid deficiency: microcytic anemia
   C. Chronic diseases: microcytic anemia
   D. Acute blood loss: normocytic anemia
3. If the total reticulocyte count is found to be increased, the most important cause of the anemia could be:
   A. Anemia due to acute blood loss
   B. Iron deficiency anemia
   C. Anemia of chronic kidney disease
   D. Anemia associated with malnutrition
4. The most specific marker for vitamin B_{12} deficiency is
   A. Methylmalonate B. Homocysteine
   C. Serum ferritin D. Hemoglobin
5. Which one of the following feeding practices is recommended for a patient with anemia?
   A. Avoiding meals from meat and poultry
   B. Avoiding orange juice immediately after meal
   C. Avoiding coffee and tea immediately after meal
   D. Avoiding foods prepare from fish
6. Which regime is not appropriate in the management of IDA?
   A. Ferrous Sulfate 325mg PO TID
   B. Ferrous gluconate 325mg PO TID
   C. Ferrous fumarate 200mg PO TID
   D. None of the above
7. One of the following statements is **correct** regarding hemophilia:

A. In hemophilia the extrinsic-pathway coagulation cascade is impaired
B. Hemophilia is an inherited autosomal dominant disorder
C. Hemophilia A is caused by the deficiency of factor IX
D. All sons born from carrier mothers will have hemophilia

8. Which coagulation test is deranged in hemophilia?
A. Prolonged Aptt B. Prolonged PT
C. Decreased platelet count D. Decreased von Willebrand factor

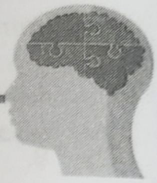
9. Desmopressin is **not** important for the management of:
A. Hemophilia A B. Hemophilia B
C. von Willebrand disease D. None of the above

10. Pain commonly occurs in patients with hemophilia. Which one of the following pharmacological agents is **not** recommended in the management of pain associated with Hemophilia?
A. Paracetamol B. Tramadol
C. Pethidine D. Diclofenac

11. The genetic inheritance pattern for hemophilia is:
A. Autosomal dominant B. Autosomal recessive
C. X-linked D. Genetic polymorphism

12. The factor deficit in hemophilia B is:
A. Factor II B. Factor VII
C. Factor VIII D. Factor IX

13. Which of the following is not considered a goal of Hemophilia therapy?
A. Prevent bleeding episodes B. Prevent long term complications
C. Eradicate inhibitors D. Arrest bleeding if it occurs



CHAPTER 7: PSYCHIATRIC DISORDERS

7.1. Schizophrenia

✍ Definitions

- ***Schizophrenia*** is a difficult term to define and is frequently misused, not only in the newspapers and movies and on television, but unfortunately among mental health professionals as well.
- Schizophrenia can be considered to be a set of symptoms in which a person's mental capacity, affective response, and capacity to recognize reality, communicate, and relate to others are impaired.
- **Diagnostic Criteria:** Two (or more) of the following, each present for a significant portion of time during a 1 – month period, at least one of these must be delusion, hallucination or disorganized speech.[1]
  a) Delusions,
  b) Hallucinations,
  c) Disorganized speech,
  d) Grossly disorganized or catatonic behavior, or
  e) Negative symptoms.

✍ Courses of the disease

- **Prodromal phase**: characterized by the gradual development of symptoms that may go unnoticed until a major symptom occurs.
  - ✓ This phase may include isolation, deterioration of hygiene, loss of interest in work or school, and dysphoria.
- **Acute phase:** This is the full-blown episode of psychotic behavior. Patients may be unable to care for themselves during this phase.
- **Stabilization phase:** The acute symptoms begin to decrease, and this phase may last for several months.
- **Stable phase:** During this phase, symptoms have markedly declined and may not be present. Nonpsychotic symptoms such as anxiety and depression may be present.

✍ Symptoms of Schizophrenia

(1) Positive Symptoms

a) **Delusions:**

i) **Persecutory:** False belief that one's self or others are being persecuted, watched or conspired against by others.

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[1] American Psychiatric Association: **Diagnostic and statistical manual of mental disorders (DSM-5®)**: American Psychiatric Pub; 2013.

ii) **Delusion of control:** False belief that one's thoughts, feelings or behaviors are controlled by an outside force.
iii) **Delusions of guilt or sin:** False belief that one has committed a terrible act.
iv) **Somatic delusions:** False belief that one's appearance or part of one's body is diseased or altered.
v) **Grandiose delusions:** Falsebelief that one has "special" power or that "supernatural knowledge"
vi) **First Rank symptoms:** *thought insertion* (experience of thoughts being put into one's mind); *thought broadcasting* (experience of one'sthoughts being known to others), *thought withdrawal* (experience of thoughts being removed from one's mind)

b) Hallucinations:

i) Auditory hallucinations: the patient experiences hearing voices from outside which will tell him to "do certain things" or two or more voices talking among each other commenting about the patient.
ii) Visual hallucinations: It is rare in functional psychoses like schizophrenia, however some schizophrenics do experience "seeing things" which are not there.

c) **Thought disorder:** Looseness of association; incoherence; neologisms; lack of abstraction; alogia; echolalia; word salad etc

(2) Negative Symptoms: **A**ffective flattening, **A**logia, **A**volition, **A**nhedonia and **A**ttentional impairment (5 A's)

(3) Cognitive Symptoms

a) Incoherence
b) Loose associations
c) Neologisms
d) Impaired attention & impaired information processing
e) Impaired verbal fluency
f) Problems with serial learning
g) Impairment in vigilance for executive functioning (decision making; mental flexibility)
h) Impaired working and secondary (storage) memory

(4) Aggressive Symptoms

a) Overt hostility
b) Self-injurious behavior
c) Sexual acting out
d) Suicide
e) Arson or other property damage

(5) Depressive & Anxious Symptoms

a) Depressed mood
b) Anxious mood
c) Tension
d) Irritability
e) Worry
f) Guilt

✍ Dopamine Pathways and the Biological Basis of Schizophrenia[1]

(1) The Mesolimbic Dopamine Pathway

- It projects from dopaminergic cell bodies in the ventral tegmental area of the brainstem to axon terminals in limbic areas of the brain, such as the nucleus accumbens.
- It is thought to have an important role in emotional behaviors.

> **Key Concepts** *Hyperactivity of the mesolimbic dopamine pathway hypothetically accounts for* ***positive symptoms*** *and* ***aggressive symtomes*** *of schizophrenia.*

(2) Mesocortical Dopamine Pathway

- It also projects from the midbrain ventral tegmental area to axons of the frontal cortex especially to *dorsolateral prefrontal cortex.*

> **Key Concepts** *DA deficiency in the mesocortical dopamine pathway hypothetically accounts for* ***the negative and cognitive symptoms in schizophrenia***

- It has been implicated in aspects of learning & memory.
- Dopamine antagonists can worsen negative symptoms of schizophrenia.

(3) Nigrostriatal Pathway

- It projects from dopaminergic cell bodies in the substantia nigra of the brainstem via axons terminating in the basal ganglia or striatum.

> **Key Concepts** *Deficiencies in DA the nigrostriatal pathway cause movement disorders, like Parkinson's disease, which is characterized by rigidity, akinesia, or bradykinesia, and tremor.*

- DA deficiency in the basal ganglia also can produce akathisia and dystonia.
- *Hyperactivity of DA* in the nigrostriatal pathway is thought to underlie various hyperkinetic movement disorders, such as chorea, dyskinesias, and tics
- Chronic blockade of DA 2 receptors in this pathway may result in a hyperkinetic movement disorder known as *Tardive Dyskinesia.*

(4) Tuberoinfundibular Dopamine Pathway

- It projects from the hypothalamus to the anterior pituitary
- It regulates prolactin secretion into the circulation.
- Dopamine inhibits prolactin secretion.

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[1] Stahl SM, Stahl SM: **Stahl's essential psychopharmacology: neuroscientific basis and practical applications**: Cambridge university press; 2013.

- Post-synaptic D2 receptor blockade by antipsychotic drugs increases prolactin secretion which produces galactorrhea, amenorrhea, sexual dysfunction, depression and osteoporosis.

✍ Antipsychotic Agents

(I) Conventional Antipsychotic Drugs

Table 7.1 Selected first generation antipsychotics[1]

Agent (dialy oral dose)	Dose Equivalent (mg)	Potency	Anti-cholinergic	Sedation	↓ BP	EPS
CPZ (200 – 1500 mg)	100	Low	4	5	5	Low
Fluphenazine (2 – 20 mg)	2	High	2	2	2	High
Haloperidol (2 – 20 mg)	2–3	High	1	2	1	High
Loxapine (20 – 200 mg)	10–15	Int.	3	3	2	Int.
Perphenazine (4 – 48 mg)	10	Int.	2	2	2	Int.
Thioridazine (200 – 800 mg)	100	Low	5	4	5	Low
Thiothixene (2 – 30 mg)	3–5	High	2	2	2	High

Scale 1–5 = low to high

- The earliest effective treatments for schizophrenia and other psychotic illnesses arose from serendipitous clinical observations rather than from scientific knowledge of the neurobiological basis of psychosis or the mechanism of action of effective antipsychotic agents.
- Thus, the first antipsychotic drugs were discovered by accident in the 1950s when a putative antihistamine (***chlorpromazine***) was serendipitously observed to have antipsychotic effects when tested in schizophrenic patients.
- Blockade of postsynaptic DA_2 receptors by a DA_2 antagonist acting in the *mesolimbic dopamine pathway* is hypothesized to mediate the antipsychotic efficacy of the antipsychotic drugs and their ability to diminish or block *positive symptoms*.
- When postsynaptic DA_2 receptors are blocked by DA_2 antagonist acting in the *mesocortical dopamine pathway*, this can cause emotional blunting and *cognitive problems* that mimic the *negative symptoms* of schizophrenia. If a

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[1] Bondi DS, Bridgeman MM, Burke JM, et al. **Updates in Therapeutics®: Pharmacotherapy Preparatory Review and Recertification Course**, 2021 ed. Lenexa, KS: American College of Clinical Pharmacy, 2021

patient already has these symptoms before treatment, medication with drugs that block these receptors can make their negative symptoms worse

- **Adverse Effects**

1) Extrapyramidal Symptoms (EPS)

- ✓ When DA_2 receptors are blocked by DA_2 antagonists in the *nigrostriatal pathway*, it produces disorders of movement like those in *Parkinson's disease*. Since the nigrostriatal pathway projects to the basal ganglia, a part of the so-called extrapyramidal nervous system, side effects associated with blockade of dopamine 2 receptors there are sometimes called *extrapyramidal symptoms* (EPS).
- ✓ Dopamine & acetylcholine have a reciprocal relationship in the nigrostriatal DA pathway. DA suppresses acetylcholine activity.
- ✓ **Four main manufestations:**

  1) Parkinsonism: This is manifested by symptoms such as bradykinesia, rigidity, tremor, or akinesia. It is usually responsive to anticholinergic agents such as diphenhydramine, trihexyphenidyl, and benztropine

  2) Dystonia: These episodes are often acute. The risk is greatest in young men and with high doses of parenteral antipsychotics. Examples include torticollis, laryngospasm, and oculogyric crisis. This is also treated with anticholinergics.

  3) Akathisia: This is a somatic restlessness and the inability to stay still or calm. Reducing the antipsychotic dose and changing to an agent with a lower incidence of akathisia are the best options, but these are not always feasible. Akathisia responds poorly to anticholinergics. Lipophilic (fat soluble) β-blockers such as propranolol and nadolol Benzodiazepines may reduce symptoms.

  4) Tardive dyskinesia: Involuntary movements that occur with long term antipsychotic therapy. Involves the orofacial muscles. Symptoms may decrease with lowering the antipsychotic dose. Changing to an agent that is associated with less tardive dyskinesia is also an option. The risk is higher with FGAs than with SGAs. Clozapine has not been associated with tardive dyskinesia. The other atypical antipsychotics also appear to have a low potential to cause tardive dyskinesia
- ✓ As DA normally suppresses acetylcholine activity, removal of dopamine inhibition causes an increase in acetylcholine activity. Thus, if dopamine receptors are blocked, acetylcholine becomes overly active. This is associated with the production of EPS
- ✓ One compensation for the overactivity of acetylcholine that occurs when dopamine receptors are blocked is to block the acetylcholine receptors with an anticholinergic agent. Thus, anticholinergics

overcome excess acetylcholine activity caused by removal of dopamine inhibition when dopamine receptors are blocked by conventional antipsychotics

2) **Endocrine effects:** Breast enlargement, galactorrhea, sexual dysfunction and menstrual changes can occur because of hyperprolactinemia caused by antipsychotics, particularly FGAs. Prolactin secretion is blocked by dopamin
3) **Neuroleptic malignant syndrome:** Occurs with all agents but appears more common with high-potency FGAs. It is manifested by agitation, confusion, changing levels of consciousness, muscle rigidity, fever, tachycardia, autonomic instability, and diaphoresis. The mortality rate is high. D/C the offending agent and give supportive therapy, including fluids and cooling. Bromocriptine and dantrolene have been used with varying success.
4) **Weight gain:** Occurs in up to 40% of patients, with low-potency agents having higher risk. Important interventions include keeping the dose as low as possible and implementing dietary management. Weight gain may occur because of actions at histamine or serotonin receptors
5) **Sexual dysfunction:** Erectile dysfunction occurs in 23%–54% of men. Loss of libido and anorgasmia may occur in men and women.

(2) Serotonin-Dopamine Antagonism

- ***Atypical antipsychotic*** is defined in part by the clinical properties that distinguish such drugs from conventional antipsychotics.
- 5HT-DA Interactions: Serotonin inhibits dopamine release, thus the release of serotonin acts as a "brake" on dopamine release. Blockade of 5HT2A receptors with an atypical antipsychotic leads to dopamine release, which compensates for dopamine deficiency.
- Therefore, atypical antipshychotics
  - a) Have stronger antagonism of 5-HT2 receptors than D2-dopamine receptors
  - b) Cause fewer EPS than conventional antipsychotics
  - c) Improve negative symptoms
  - d) Improve positive symptoms as well as do conventional antipsychotics.
- ***Clozapine:*** It is indicated only for treatment-resistant schizophrenia (defined as lack of response to two or more adequate trials of antipsychotics, including at least one FGA and one SGA). Clozapine is the only antipsychotic indicated for reducing suicidal thinking in patients with schizophrenia or schizoaffective disorder. Clozapine is not associated with EPS or tardive dyskinesia, and it may be more effective at reducing negative symptoms than FGAs.

- ✓ Adverse effects include (a) **severe neutropenia (agranulocytosis):** this is the most limiting adverse effect. It can lead to a dramatic drop in neutrophils, which increases the risk of serious or fatal infections. It is defined as an absolute neutrophil count (ANC) less than 500 cells/mm3. The incidence is about 0.9% and is highest during the first 4–6 months of therapy. (b) **OH**, **bradycardia, syncope**, and **cardiac arrest**: is dose related and at highest risk at initiation of therapy or with rapid dose titration. Must be initiated at 12.5 mg once or twice daily, titrated slowly, and given in divided doses (c) **seizures**: Risk is dose related and can be minimized by starting low andtitrating slowly. (d) myocarditis and cardiomyopathy
- ✓ Dosage: must be initiated at 12.5 mg once or twice daily, titrated slowly, and given in divided doses. The usual effective treatment range is 400 to 500 mg a day.
- ✓ Lab monitoring: weekly WBCs for the first 6 months and then every 2 weeks. Clozapine should be discontinued if the granulocyte count is less than 1000 per mm3.

- ***Risperidone:*** It has the simplest pharmacologic profiles and comes closest to an SDA. It is atypical at lower doses but can become more "conventional" at high doses in that EPS can occur. It probably has no advantage in patients requiring high doses of antipsychotics. It has favored uses, not only in schizophrenia at moderate doses but also for conditions in which low dose of typical antipsychotics have been used in the past (for elderly pts and children). A long-acting intramuscular formulation (Risperdal Consta) is available that is better tolerated than the other intramuscular depot forms of antipsychotics. It is administered every 2 weeks and requires a 3-week bridge therapy with oral risperidone. Adverse effects include sedation, OH, weight gain, sexual dysfunction, and hyperprolactinemia.
- ***Olanzapine:*** It has a chemical structure related to clozapine. Unlike clozapine, however, it has not been associated with agranulocytosis. It is atypical because it lacks EPS not only in smaller dosage but also at higher dosage. It lacks the extreme sedating properties of clozapine. Together with clozapine, olanzapine carries the highest risk of diabetes. It is associated with **weightgain** because of its antihistaminic and serotonin 2C antagonist properties It is highly effective in the treatment of the negative symptoms because of its antagonism on 5HT2A receptors on the dopamine neurons
- ***Quetiapine:*** In addition to antagonism at the D2 and serotonin-2 receptors, it has a high affinity for histamine-1 receptors. For this reason, it has a high incidence of somnolence and weight gain. May also cause OH.

Implicated in the development of new-onset type-2 diabetes. No report of tardive dyskinesia or prolactin elevation.

- ***Ziprasidone***
  - ✓ It has a low incidence of metabolic syndrome, but can prolong the QTc interval. Use caution if combining it with other drugs (e.g., tricyclic antidepressants [TCAs] or antiarrhythmics) that can also increase the QTc interval. The recommended adult starting dose of oral ziprasidone is 20 to 40 mg twice daily.
- ***Aripiprazole***
  - ✓ Aripiprazole acts as a partial agonist at dopamine D2 receptors. The drug is also a partial agonist at serotonin 5HT1a receptors, but an antagonist at 5HT2a, H1, and alpha-1-adrenergic receptors. Has a low risk of most forms of EPS, including tardive dyskinesia. It is associated with a high incidence of akathisia.

Table 7.2 Adverse Effects of SGAs[1]

Drug	Metabolic syndrom			Cardiac	Sedation
	Weight Gain	DM	Dyslipidemia		
Aripiprazole	Little to none	No	Little to none	None	Low
Clozapine	Highest	High	High	OH, prolonged QTc tachycardia	High (antichol)
Olanzapine	Highest	High	High	None	High (antichol)
Paliperidone	Low	Low	None	Possible QTc prolongation	None
Quetiapine	Moderate	Moderate	Moderate	OH	High (antichol)
Risperidone	Moderate	Moderate	Less	OH	Low
Ziprasidone	Little	No	Less	Prolonged QTc	Low

OH-orthostatic hypotension, DM-diabetes mellites

✍ Initial Management of Schizophrenia

- **First episode of psychosis:** Patients with a first episode of psychosis be treated with an antipsychotic at the lower end of the recommended dose range. For example, for a first episode of psychosis, it is recommend starting **aripiprazole** at 5 mg per day or **risperidone** starting at 1 mg per day These can be increased over one week to the lower end of the therapeutic range (ie, 10 mg per day aripiprazole, 2 mg per day risperidone) while monitoring for response. **Preference for second-generation agents** – first-line treatment in most cases of psychosis, because fewer EPS (ie, akathisia, dystonia, parkinsonism) than 1st-generation antipsychotics ***aripiprazole*** or ***risperidone*** are appropriate choices due to their relatively favorable side effect profiles. ***Clozapine*** is more effective than other agents, it is reserved for patients who have not responded to other antipsychotics because. It has significant side effects and medical risks that require careful monitoring

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[1] Bondi DS, Bridgeman MM, Burke JM, et al. **Updates in Therapeutics®: Pharmacotherapy Preparatory Review and Recertification Course**, 2021 ed. Lenexa, KS: American College of Clinical Pharmacy, 2021

- **Negative symptoms**: most classes of medications tested have not shown clinically meaningful effects on negative symptoms. **Cariprazine** has shown positive effects in a clinical trial. Small reductions in negative symptoms were found for SGAs, antidepressants, glutamatergic agents, and combinations of these medications, but not for first-generation antipsychotics or brain stimulation
- **Agitation**: is a psychiatric emergency. Agitation is a state of motor restlessness or excitement and is often accompanied by mental tension and irritability. Treatment with an antipsychotic with prominent sedating effects, such as **olanzapine** 5 to 10 mg disintegrating tablet or haloperidol 2 to 10 mg orally is suggested. For severely agitated patients: a **benzodiazepine** in combination with the antipsychotic, the combination of haloperidol 5 mg, lorazepam 2 mg, and benztropine 2 mg given IM
- **Insomnia**: For insomnia due to underlying psychosis, an antipsychotic with sedating properties is suggested. An example is **quetiapine**, which can be initiated at 25 mg twice daily and increased every few days by 25 mg twice daily to an initial target dose of 300 to 400 mg daily, depending on response
- **Psychosis due stimulant intoxication**: When the underlying cause of psychosis or agitation is thought to be stimulant related, initial treatment with a **benzodiazepine** rather than an antipsychotic medication. For example, lorazepam can be given at a dose of 2 to 4 mg IV and repeated every 10 minutes. In milder cases, it may be given orally or IM.
- **Patients with or at risk for metabolic syndrome**: For patients with diabetes, obesity, dyslipidemia, or other uncontrolled cardiovascular risks, choosing an agent that has a lower risk of metabolic side effect is preferred
- **Patients at risk for QT prolongation**: avoid ziprasidone, quetiapine, chlorpromazine, and IV haloperidol, Patients with metabolic disorders such as hypokalemia or hypomagnesemia, patients with anorexia nervosa, and patients on other medications that can prolong QT intervals, such as antiarrhythmics. Monitor ECG at baseline, at three months, and yearly.
- **Catatonia**: Antipsychotic medications should be avoided as they can precipitate or worsen catatonia. Catatonia is a syndrome manifested by inability to move normally. It can present as either extreme negativism (eg, passive resistance to movement), mutism, or catatonic excitement (eg, excessive, purposeless motor activity). First-line treatment for catatonia is a benzodiazepine or electroconvulsive therapy (ECT),

Administration

- **Initial dosing** — In adults, most antipsychotic medications should be titrated from the initial dose to the therapeutic range as quickly as tolerated. Exceptions include older patients, patients with first episode of psychosis, and patients with relevant medical comorbidities. Should be started at a lower dose and titrated slowly. These patients may be more sensitive to side effects from medications.
- **Expected response** — Resolution of psychotic symptoms generally begins within several days of reaching an effective dose It may take as much as four to six weeks for full improvement. Most patients who will improve on an antipsychotic show the most rapid improvement during the first two weeks. If the patient shows only minimal response to an antipsychotic during the first two weeks, it is unlikely that the individual will have a robust response.
- **Adjustments for poor response to initial treatment** — If there is no improvement in psychotic symptoms after two to four weeks of a therapeutic dose, changing to a different antipsychotic medication is recommended. Switching antipsychotics can be helpful when a poor response is related to side effects. For patients who are actively psychotic who are switching from an ineffective medication to another choice, maintaining full dose of the current medication as the new medication is increased. Once the second medication has reached its target dose, the first medication may be gradually decreased and discontinued. Patients who have not responded adequately to two or more trials of antipsychotics at therapeutic dose (eg, >600 mg chlorpromazine or its equivalent) are considered **treatment resistant**
- Duration of pharmacologic therapy — The recommended duration of antipsychotic therapy varies according to the underlying etiology: In chronic schizophrenia, antipsychotics should be offered indefinitely to reduce the risk of relapse. With time-limited psychoses, antipsychotic therapy can be continued for two weeks after the resolution of symptoms and then tapered off gradually

Treatment-resistant schizophrenia

> **Key Concepts** ***Treatment-resistant schizophrenia**: at least two trials of ≥6 weeks at a therapeutic dose (equivalent to ≥600 mg chlorpromazine) with adherence ≥80% of prescribed doses.*

- Management of patients with treatment-resistant schizophrenia includes the determination of clozapine eligibility, treatment with clozapine (preferably) or an alternative, and for patients who continue to respond inadequately, trials of other interventions with lesser evidence supporting efficacy.
- **Clozapine** — To be eligible for a clozapine trial, a patient with treatment-resistant schizophrenia should additionally meet the following criteria: absolute neutrophil count ≥1500 cells/microliter, the benefits of clozapine outweighing

the risks, ability to adhere to treatment monitoring and patient/family agreement. Alternatives for patients ineligible for or refusing clozapine

- ✓ Electroconvulsive therapy (ECT) (preferred)
- ✓ Lamotrigine, topiramate, minocycline
- ✓ Repetitive transcranial magnetic stimulation (rTMS)

✍ **Maintenance therapy**

- The goal of maintenance treatment of schizophrenia is to minimize symptoms and functional impairments, minimize side effects of pharmacotherapy, avoid relapses, and promote recovery that allows self-determination, full integration into society, and pursuit of personal goals.
- **Full response to pharmacologic therapy**: If a patient has fully responded (i.e, no longer has clinically significant psychosis) to the antipsychotic initiated for an acute psychotic episode, we continue that medication. We use the lowest effective dose.
- **Partial response or recurrence of symptoms:** Have persistent residual symptoms (eg, incomplete or partial response or intermittent symptom recurrenc:
  - ✓ Assess medication adherence
  - ✓ Subtherapeutic doses: increase their dose until either the patient responds, therapeutic range is reached, or side effects limit further increase
  - ✓ In the therapeutic range: switching the medication

Key Concepts ***Duration of antipsychotic therapy:*** *For patients with known or suspected schizophrenia who have recovered from an acute first psychotic episode, continuing antipsychotics for* ***at least two to three years*** *is recommended. For those who had psychosis that was extremely disruptive, difficult to control, or accompanied by violence or suicidal ideation, continuing antipsychotic therapy* ***indefinitely*** *is favorable. For those who have had multiple episodes of psychosis in the past, continuing antipsychotic therapy* ***indefinitely*** *is recommended.*

7.2. Depression

✍ Epidemiology

- Globally, over 300 million people are estimated to suffer from depression in 2015, equivalent to 4.4% of the world's population. Depression is more common among females (5.1%) than males (3.6%). The prevalence of depression was estimated to 4.7% (4.5 million) in Ethiopia in 2015.[1]
- Depression occurs in all age, racial, ethnic & socioeconomic groups.

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[1] World Health Organization: **Depression and other common mental disorders: global health estimates**. In.: World Health Organization; 2017.

- Prevalence of depression is more in medically ill patient than the general population.
- Depression is episodic, with untreated episodes commonly lasting 6 to 24 months, followed by recovery or remission

✍ Diagnostic Criteria for MDD[1]

- Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
  1) Depressed mood most of the day, almost everyday (feels sad or empty, appears tearful)
  2) Loss of interest or pleasure in usual activities (anhedonia)
  3) Decreased energy or increased fatigability
  4) Loss of confidence or self-esteem
  5) Unreasonable feelings of guilt, feelings of worthlessness
  6) Recurrent thoughts of death or suicide
  7) Complaints of diminished ability to think or concentrate
  8) Change in psychomotor activity, with agitation or retardation
  9) Sleep & appetite disturbances

✍ Etiology & Pathogenesis of Depression

- Neurobiological factors
- Psychosocial factors
- Developmental factors
- Monoamine hypothesis: depresssion is caused by neurotransmitter deficiency

✍ Treatment of Depression

- Treatment goals:
  - ✓ Restore role/function
  - ✓ Reduce/remove sign and symptoms
  - ✓ Minimize relapse and recurrence
- When treatment of depression results in removal of essentially all symptoms, it is called *remission* for the first several months, and then *recovery* if it is sustained for longer than 12 months. Such patients are not just better – they are well.
- When depression returns before there is a full remission of symptoms or within the first several months following remission of symptoms, it is called a *relapse*. When depression returns after a patient has recovered, it is called a *recurrence*.

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[1] American Psychiatric Association: **Diagnostic and statistical manual of mental disorders (DSM-5®)**: American Psychiatric Pub; 2013.

- **Classes of antidepressants**

1) Tricyclic antidepressants (TCAs)

✓ TCAs are effective, but adverse effects have limited their use. Now that newer agents with more tolerable adverse effect profiles are available, TCAs are used less often. TCAs have several uses such as treatment for pain syndromes, migraine prophylaxis, and anxiety disorders

✓ TCAs have α-adrenergic blockade, antihistaminic, and anticholinergic effects, leading to orthostasis, sedation, and anticholinergic symptoms (Dry mouth, urinary retention, constipation, tachycardia, & blurred vision), respectively. TCAs can cause sexual dysfunction. TCAs can be cardiotoxic in overdose. They cause seizures and torsades de pointes. An actively suicidal patient should not receive a TC The antidepressant effect of the TCAs is attributed to their inhibition of NE & 5-HT transporters.

Examples	Initial dose	Max dose
Amitriptyline	30–75 mg	300mg
Clomipramine	10 mg daily	250mg
Doxepin	75 mg daily	300mg
Imipramine	75 mg daily	300mg
Nortriptyline	75 mg daily	150mg
Trimipramine	50 mg daily	300mg

✓ These drugs are not recommended in patients with cardiac disease or seizure disorders. A withdrawal syndrome occurs if these drugs are discontinued too quickly. Symptoms reflect the reversal of anticholinergic effects and include lacrimation, nausea, and diarrhea, with insomnia, restlessness, and possible balance problems. Gradual dose reductions help reduce these symptoms.

Table 7.3 Adverse effect profile of the commonly used TCAs

Drug	Anticholinergic	Sedation	OH	Cardiotoxicity
Amitriptyline	High	High	Moderate	High
Imipramine	Moderate	Moderate	High	High
Desipramine	Low	low	Moderate	Moderate
Nortriptyline	Moderate	Moderate	Low	Moderate

2) Monoamine Oxidase Inhibitors

✓ The action of MAOI is to increase the availability of the monoamine neurotransmitter NE, DA, and 5-HT by blocking their metabolism.

- ✓ The classical MAOI are non-selective & irreversible (Phenelzine, Tranylcypromine, & Isocarboxazid). The newer ones are selective and reversible
    - ⇨ Reversible inhibitor of MAO-A (Moclobemide)
    - ⇨ Selective inhibitor of MAO-B (Deprenyl)
- ✓ Despite their efficacy, their clinical use has been limited due to the life threatening "hypertensive crisis" when they are ingested with certain food or medications (tyramine, sympathomimetics etc.). Another untoward drug-drug interaction is the so-called serotonin syndrome if it is co-administered with SSRIs, TCAs & some of the newer antidepressant. Other side effects of MAOI include dizziness, orthostatic hypotension, suppression of REM sleep, weight gain & sexual dysfunction.

3) Selective Serotonin Reuptake Inhibitors (SSRIs)

- ✓ SSRIs selectively inhibit the reuptake of serotonin into the presynaptic neuron and desensitize the presynaptic serotonin autoreceptor, resulting in increased serotonin concentrations. The FDA has approved six SSRIs for the treatment of depression: **fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram,** and **escitalopram**.
- ✓ The efficacy of SSRIs is equal for treatment of depression. The most common adverse effects associated with this class of agents include GI complaints, insomnia, restlessness, headache, and sexual dysfunction.

> **Key Concepts** ***Sexual dysfunction*** *may occur in 50% or more of patients receiving SSRIs. Some interventions to consider for SSRI-induced sexual dysfunction in both sexes include using the wait-and-see method, adding bupropion for the treatment of sexual dysfunction, and lowering the SSRI dose. Sildenafil may be beneficial for men.*

- ✓ Because these drugs have potent serotonergic activity, combinations with other drugs affecting serotonin can lead to **serotonin syndrome**. Examples include MAOIs, dextromethorphan, meperidine, sympathomimetics, triptans, lithium, TCAs, and SNRIs. Serotonin syndrome includes symptoms from three clusters: neuromuscular hyperactivity (e.g., myoclonus, rigidity, tremors, incoordination), altered mental status (agitation, confusion, hypomania), and autonomic instability (hyperthermia, diaphoresis). Serotonin syndrome can be subtle in onset or be confused with neuroleptic malignant syndrome. Treatment includes discontinuing the offending agent, providing supportive measures such as cooling blankets and respiratory assistance, and providing clonazepam for myoclonus, anticonvulsants for seizures, and nifedipine for hypertension.

Examples	Initial dose	Max dose
Citalopram	20 mg daily	40 mg daily
Escitalopram	10 mg daily	20 mg daily
Fluoxetine	20 mg daily	60 mg daily
Fluvoxamine	50 mg daily	300 mg daily
Paroxetine	20 mg daily	50 mg daily
Sertraline	50 mg daily	200 mg daily

- ✓ A **withdrawal syndrome** has been observed, especially for the drugs with shorter half-lives, so a gradual dose reduction (e.g., over 2–4 weeks) may be indicated. Symptoms include flu-like symptoms, such as nausea and chills, and neurologic symptoms, such as paresthesias, insomnia, anxiety, and "electric shock"–type sensations. If the problem is severe or persists, the SSRI can be reinitiated and the dose gradually reduced again. It is most common with paroxetine, which has the shortest half-life; is less common with sertraline; and even less likely with fluoxetine, which has the longest half-life.

4) Norepinephrine & Dopamine Reuptake inhibitor

- ✓ ***Bupropion*** is the prototypical agent of the NE & dopamine reuptake inhibitors. It boosts norepinephrine & dopamine in the synapse. It is used also as augmenting agent. Most common side effects include anxiety, agitation, decreased appetite & insomnia. The most dangerous SE of bupropion is its increase in **seizure** risk. Other applications of bupropion are for ADHD & treatment of smoking cessation.

Key Concepts *No weight gain and sexual dysfunction associated with* ***bupropion****.*

5) Serotonin & Norepinephrine Reuptake Inhibitors

- ✓ ***Venlafaxine***, ***desvenlafaxine*** and ***duloxetine*** block the reuptake of norepinephrine and serotonin. Unlike TCAs, they have negligible effects at other receptors that cause anticholinergic or antihistaminic adverse effects, with the possible exception of duloxetine, which appears to have a slightly higher incidence of anticholinergic symptoms. At doses less than 150 mg/day, venlafaxine is a serotonin reuptake inhibitor.
- ✓ The most common side effects are nausea, anorexia, insomnia, nervousness, sexual dysfunction and increase in BP (dose-dependent). Abrupt D/C of venlafaxine can lead to a withdrawal syndrome similar to that with the SSRIs

6) Mixed Serotonergic Medications

- ✓ Includes vilazodone, trazodone, nefazodone, mirtazapine

- **Initiating, Adjusting, and Monitoring Therapy**

✓ Three phases of therapy:

1) Short term (acute): The goal of this phase is **remission**, which may take 12 weeks. Remission is defined as at least 3 weeks with no symptoms of depressed mood and anhedonia and no more than three remaining symptoms of depression.

> **Key Concepts** ***SSRIs*** *are the most widely prescribed class of antidepressant. Alternatives: second-generation antidepressants, such as serotonin-norepinephrine reuptake inhibitors, atypical antidepressants, and serotonin modulators.*

Pharmacogenetics: Genetic factors may influence antidepressant pharmacokinetics, including metabolism, which in turn can affect the dose required to achieve a therapeutic serum concentration. Patients may rapidly metabolize drugs due to genetic polymorphisms of hepatic enzymes and thus require larger doses. Reviews have noted that the prevalence of increased CYP2D6 metabolism in different racial and ethnic groups was as follows: African Americans – 5%, Asian Americans – rarely seen, Ethiopians (blacks) – 16 to 29%, Saudi Arabians – 20%, Whites: Spain – 7 to 10%, Sweden – 1 to 2%, United States – 4%.

2) Continuation: The goal of this phase is to keep the symptoms in remission using full-dose therapy. This phase usually continues for 4–9 additional months to keep the patient in remission.

3) Maintenance: Long-term therapy at full doses may be required in patients at high risk of relapse, including prior episodes of depression or a strong family history of relapse. The duration of this phase is determined on an individual basis.

✓ When one drug has failed, another agent from another class is often tried. However, some patients who do not respond to one SSRI may respond to another, and this is a reasonable option. ***Treatment resistance*** is defined as failing to respond to two or more agents from different classes. At this point, **ECT**, augmentation therapy, or combination therapy can be considered if they have not been used already.

✓ Treatment-resistant depression (augmentation therapy): SGAs (or atypical antipsychotics) are commonly used as adjuncts to antidepressant therapy. In addition, ketamine infusion, lithium, liothyronine, scopolamine and buspirone are indicated

- **Switching Antidepressants**

✓ **Direct switch**: Some patients can switch directly from one SSRI to another SSRI, e.g., from venlafaxine to duloxetine. Exception: patients switching from **fluoxetine** should wait 4 to 7 days because of its long half-life, then start a low dose of another SSRI.

- ✓ **Cross-tapering**: Gradually reducing the dose of the old drug, while simultaneously increasing the dose of the new one works well. Recommended this when switching to meds with a different mechanism, such as switching from an **SSRI** to **bupropion** or **mirtazapine**.
- ✓ **A wash-out period** is necessary when switching to or from an **MAO inhibitor**.

7.3. Bipolar Disorder

✍ Definition

- Bipolar disorder is the experience of a manic or hypomanic episode. Mania can be thought of as the affective opposite of depression. A **manic** episode is characterized by at least 1 week of an abnormal and persistently elevated mood accompanied by an increased amount of activity. Other symptoms include inflated self-esteem, irritability, decreased need for sleep, pressured speech, flight of ideas, poor attention, increased hyperactivity or agitation, and involvement in high-risk, pleasurable activities without respect to the consequences.[1] A **hypomanic** episode is a milder form of mania. It must exist for 4 days or longer. Unlike mania, it is not severe enough to warrant hospitalization, does not impair social or occupational functioning, and is not associated with psychosis
- Two types of bipolar disorder (I and II). (1) **Bipolar I**: Chronic disorder marked by one or more manic or mixed episodes and major depressive episodes. (2) **Bipolar II:** Chronic disorder marked by one or more major depressive episodes, accompanied by at least one hypomanic episode.
- **Cyclothymic disorder**: Several periods of hypomania and mild depression, none of which meet the criteria for mania or major depressive episode
- **Rapid cycling**: At least four episodes of mania or depression in 1 year.
- Bipolar disorder, particularly type II bipolar disorder, is often misdiagnosed as major depression. The diagnosis is important because the two conditions are treated differently.

✍ Prevalence

- The occurrence rate in men & women is similar, the life-time prevalence of bipolar disorder to be 1.6% & 1.3% respectively. Bipolar disorder in female patients has been associated with relatively predominant depressive, rather than manic, features. Period of onset appears to be during adolescence (15-19). The life time risk of death by suicide is approx. 19%.

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[1] American Psychiatric Association: **Diagnostic and statistical manual of mental disorders (DSM-5®)**: American Psychiatric Pub; 2013.

Etiology and Pathophysiology

- Genetics
  - ✓ Family linkage studies have shown that bipolar disorder is substantially genetical.
  - ✓ Concordance rates for bipolar disorder have been estimated to be up to 90% for monozygotic twins & 14% for dizygotic twins.
- It is probably mediated through multiple NT pathways and biological interactions. Several neurotransmitters including ***NE, DA, glutamate,*** & ***GABA*** have been implicated in bipolar disorder to some degree (L-dopa, amphetamine, & *cocaine* have been found to precipitate mania in non-bipolar individuals)

Treatment

- Currently there are several mood stabilizers: lithium, sodium valproate, olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, and lamotrigine

I) Lithium

- ✓ Lithium continues to be the gold standard for treating type I bipolar disorder. It is effective for the manic and depressive components. Although it is not a particularly good antidepressant as monotherapy in unipolar depression, it is effective in patients with bipolar disorder. Lithium also has anti-suicidal effects when used to treat bipolar disorder. ***Antimanic effects*** can occur in 1–2 weeks. Most clinicians use antipsychotics or benzodiazepines as adjunctive therapy during this period to cover the agitation and other symptoms. ***Antidepressant effects*** may take 6–8 weeks.
- ✓ Initial dosing is 600–900 mg/day in divided doses and then titrated according to response and tolerability. Maintenance doses are based on serum concentrations, symptom relief, and the occurrence of adverse effects. A pre-lithium workup includes CBC, electrolytes, renal function, thyroid function tests, urinalysis, ECG, and pregnancy test for women of childbearing age.

Key Concepts ***Monitoring for lithium.*** *Serum concentrations must be monitored. Perform renal function tests, thyroid function tests, and a urinalysis every 6–12 months*

- ✓ Pregnancy: Lithium is teratogenic, particularly in the first trimester. Women of childbearing age should be counseled on its potential effects.
- ✓ Adverse effects are common with lithium, particularly during therapy initiation or after dose changes.
  - i) **Rash or ↑ psoriasis:** discontinue the drug temporarily or permanently
  - ii) **Tremor**: reduce dose (Cp); add β-blocker

iii) **CNS toxicity** (e.g., agitation, confusion): reduce dose (Cp)
iv) **GI** (nausea, vomiting, diarrhea): reduce dose; try extended-release product, split doses
v) **Hypothyroidism**: discontinue Li or give levothyroxine
vi) **Polydipsia or polyuria**: Reduce dose, manage intake, and try amiloride or HCTZ, but HCTZ will ↑ Li Cp; single bedtime dosing helps
vii) **Interstitial fibrosis, glomerulosclerosis**: Keep dose at lowest effective concentration; avoid dehydration
viii) **Teratogenicity**: Avoid during first trimester, if possible

2) **Anticonvulsants for Bipolar Disorder**

✓ **Valproate**: As effective as lithium in acute and prophylactic management. It appears to be good for rapid cyclers but may not be as effective during depressive episodes. It is also beneficial for patients with dysphoric mania, mixed episodes, or a history of substance use disorder. Toxicity can happen by co-administering with highly protein-binding drugs (e.g. aspirin). Side effects include: sedation, GI distress, benign hepatic transaminase elevation, weight gain, hair loss, and rarely acute pancreatitis (in children), & polycystic ovary disease. Use in pregnancy has been associated in neural tube defects in the fetus. Dosing: 1) in mild forms, start with 250 mg po tid and increase the dosage as needed till the patient stabilizes. 2) in acute mania: load the patient up to 20mg/kg/day.

✓ **Carbamazepine**: Effective for acute mania and maintenance therapy, particularly in patients with a history of head injury. Carbamazepine can abe added to lithium for patients who have not responded to monotherapy.

✓ **Lamotrigine**: It appears particularly effective for the prevention of future depressive episodes of bipolar disorder. It is less effective than other mood stabilizers for the prevention of the manic phase. A Stevens-Johnson type rash occurs in about 0.3% of adults and 1% of children. The dose titration must be halved if lamotrigine is given with valproate and doubled if given with carbamazepine because of increased lamotrigine metabolism. Lamotrigine has been associated with aseptic meningitis in adult and pediatric patients.

✓ **Other anticonvulsants**, including levetiracetam, oxcarbazepine, and topiramate, are used for bipolar disorder, but data regarding their efficacy are scarce

3) **Antipsychotics for Bipolar Disorder**

✓ Antipsychotics, particularly SGAs, have mood-stabilizing properties. They can be used alone or with anticonvulsant mood stabilizers to treat bipolar symptoms. Metabolic adverse effects associated with